IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Johannes BARTHOLOMÄUS et al.

US Patent Application Serial No.: 10/718,1

12 (US 2005-0031546 A1)

Title: Abuse-proofed dosage form

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DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents

Washington, D.C. 20231

Sir:

I, Heinrich Kugelmann, residing at Blücherplatz 7, 52068 Aachen, a citizen of Germany, declare that:

I am a pharmacist and joined Grünenthal GmbH, Aachen Germany, on August 1, 1981. Since 1981 I have been employed by that company in the department Pharmaceutical Development, since 2005 as group leader New Therapeutic Entities Research.

I am familiar with the field of medical dosage forms, and am one of the inventors of U.S. Patent Application Serial No. 10/718,112.

Further and subsequently to the experiments summarized in my affidavit dated February 6, 2009, the following experiments have been conducted under my supervision and control:

The following master batches were manufactured by mixing all components:

[mg]	#1	#2	#3	#4	#5	#6
Tramadol-HCl	500.0 mg	500.0 mg	500.0 mg	500.0 mg	500.0 mg	500.0 mg
Polyethylene oxide M_w 7,000,000 g/mol	-	100.0 mg	200.0 mg	300.0 mg	1400.0 mg	2800.0 mg
Total weight of composition	500.0 mg	600.0 mg	700.0 mg	800.0 mg	1900.0 mg	3300.0 mg
[wt.-%]						
Tramadol-HCl	100.0 %	83.3 %	71.4 %	62.5 %	26.3 %	15.2 %
Polyethylene oxide M_w 7,000,000 g/mol	0 %	16.7 %	28.6 %	37.5 %	73.7 %	84.8 %

Thus, master batch #1 consisted of pure Tramadol-HCl, whereas master batches #2 to #6

additionally contained increasing amounts of polyethylene oxide (from 16.7 to 84.8 wt.-%).

When comparing the breaking strength of different tablets, it is necessary that the overall weight of the tablets is kept constant, in the present case at 150 mg. For that purpose, 450.0 mg were taken from each of the above master batches #1 to #6 and divided into three identical portions of 150.0 mg (three portions of 150.0 mg = 450.0 mg).

A tabletting tool with top punch, bottom punch and die for tablets with a diameter of 7 mm was heated to 80 °C in a heating cabinet. The 150 mg portions derived from the master batches were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets (mean value for three tablets made from identical portions, n=3) was determined with the apparatus and method in accordance with US 10/718,112.

The results of the breaking strength measurement are summarized here below:

[wt.-%]	#1	#2	#3	#4	#5	#6
Tramadol-HCl	100.0 %	83.3 %	71.4 %	62.5 %	26.3 %	15.2 %
Polyethylene oxide M_w 7,000,000 g/mol	0 %	16.7 %	28.6 %	37.5 %	73.7 %	84.8 %
Breaking strength [N]	< 500 N	< 500 N	< 500 N	< 500 N	**> 500 N**	**> 500 N**

The tablets with a breaking strength > 500 N (made from the portions derived from master batches #5 and #6) could not be comminuted using a hammer, nor with the assistance of a mortar and pestle.

From the above data I conclude that the polyethylene oxide must be employed in a sufficient quantity to yield tablets having a breaking strength of at least 500 N. If the quantity of the polyethylene oxide is too low the desired breaking strength cannot be achieved.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Aachen, Germany, Juli 2, 2009

Heinrich Kugelmann